SPECTRUM PHARMACEUTICALS Redefining Cancer Care

URGENT: LEVOLEUCOVORIN UPDATE

February 1, 2011

Dear Healthcare Professional:

Due to the ongoing critical shortage of Leucovorin Calcium for Injection in the United States market, Spectrum Pharmaceuticals, Inc. (Spectrum) is working with the United States Food and Drug Administration (FDA) to increase the availability of levoleucovorin products. Levoleucovorin is the levo isomeric form of racemic *d,l*-leucovorin, present as the calcium salt, and is the pharmacologically active isomer of leucovorin [(6-S)-leucovorin]. **Levoleucovorin is dosed at <u>one-half</u> the usual dose of leucovorin.**

Due to the shortage of both leucovorin and FUSILEV® (levoleucovorin) for Injection, the FDA has authorized Spectrum to import **Levoleucovorin 100 mg Powder for Injection** manufactured by Pfizer Inc. (previously known as Wyeth) into the US market from Italy. **Pfizer Levoleucovorin 100 mg Powder for Injection** is manufactured in an FDA-inspected facility (Pfizer in Catania, Italy). This facility has been in compliance with FDA manufacturing standards.

No other entity except for Spectrum is authorized by FDA to import or distribute **Pfizer Levoleucovorin 100 mg Powder for Injection** in the United States. Any sales of **Pfizer Levoleucovorin 100 mg Powder for Injection** from any entity other than Spectrum will be considered a violation of the Federal Food, Drug and Cosmetic Act and will be subject to enforcement by FDA.

Effective immediately, Spectrum will offer two versions of Levoleucovorin for Injection:

	FUSILEV® (levoleucovorin) for Injection	**Pfizer Levoleucovorin 100 mg Powder for Injection**
50 mg Glass Vial	NDC 68152-101-00	Not Available
100 mg Glass Vial	Not Available	A.I.C. n. 024659195

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Pfizer Levoleucovorin 100 mg Powder for Injection contains the same active ingredient, levoleucovorin calcium, as FUSILEV® (levoleucovorin) for Injection and is an acceptable substitute for FUSILEV®. **It is important to note that there are some key differences in the formulation and labeling between the US marketed FUSILEV® and the international Pfizer Levoleucovorin 100 mg Powder for Injection:**

- The **Pfizer Levoleucovorin 100 mg Powder for Injection** product contains twice the amount of levoleucovorin as Spectrum's FUSILEV® (levoleucovorin) for Injection. Spectrum's FUSILEV® contains 50 mg levoleucovorin and 50 mg mannitol per vial, whereas the **Pfizer Levoleucovorin 100 mg Powder for Injection** product contains 100 mg levoleucovorin and 100 mg mannitol per vial. Both products may contain hydrochloric acid and/or sodium hydroxide for adjustment of pH.

- The **Pfizer Levoleucovorin 100 mg Powder for Injection** product that will be distributed in the United States will contain labeling (vial, unit carton, and package insert) that appears in English. This English text is a certified word-for-word translation of the original Italian text in the labeling for the **Pfizer Levoleucovorin 100 mg Powder for Injection** product. In the Italian version, the product is refered to as "calcium levofolinate." The active ingredients of the two products are the same.

- The contents of the **Pfizer Levoleucovorin 100 mg Powder for Injection** vial are reconstituted with 10 mL of sterile water for injection. FUSILEV® (levoleucovorin) for Injection is reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection, USP. Both preparations yield a levoleucovorin concentration of 10 mg per mL.

- There are differences in the approved indications for FUSILEV® (levoleucovorin) for Injection and **Pfizer Levoleucovorin 100 mg Powder for Injection**.

    - FUSILEV® rescue is indicated after high-dose methotrexate therapy in osteosarcoma. FUSILEV® is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists. FUSILEV® is not approved for pernicious anemia and megaloblastic anemias secondary to the lack of vitamin B_{12}. Improper use may cause a hematologic remission while neurologic manifestations continue to progress.

    - **Pfizer Levoleucovorin 100 mg Powder for Injection** is approved in Italy for use in combination with fluoropyrimidine in the treatment of metastatic colorectal cancer with a palliative intent, in precautionary (adjuvant) treatment of radically operated colorectal cancer, and in the "rescue" from high doses of methotrexate or other similar drugs.

- The original barcode has been omitted from the label of the **Pfizer Levoleucovorin 100 mg Powder for Injection** product for US distribution since the barcode is an

international pharmaceutical manufacturing code and may not be appropriately recognized by scanning systems used in the United States.

- Special caution should be taken to assure that the correct drug product is being prepared and administered to individual patients according to directions in the package insert.

The product comparison table below also highlights the differences between FUSILEV® (levoleucovorin) for Injection and the **Pfizer Levoleucovorin 100 mg Powder for Injection**.

(For Online Version: Please click here for package inserts: Spectrum FUSILEV & Pfizer Levoleucovorin 100 mg Powder for Injection)

To further supplement supply, Spectrum maintains its commitment to expedite the manufacturing of FUSILEV® to maintain continuous releases of the product.

Please evaluate the use of **Pfizer Levoleucovorin 100 mg Powder for Injection** in your institution. If your institution is not willing to use **Pfizer Levoleucovorin 100 mg Powder for Injection**, you may continue to order FUSILEV®. Spectrum will continue to fill those orders through the allocation process. Customers have the following options when ordering FUSILEV® or **Pfizer Levoleucovorin 100 mg Powder for Injection**:

- Wholesalers can place drop ship orders on a customer's behalf directly with Spectrum.
- Customers can order directly from Spectrum by contacting Customer Service at 1-877-FUSILEV (1-877-387-4538) between 8 a.m. –5p.m. Central Standard Time.
- **Pfizer Levoleucovorin 100 mg Powder for Injection** will be covered under Spectrum's Return Goods Policy.

Until further notice, all levoleucovorin products, including FUSILEV® and **Pfizer Levoleucovorin 100 mg Powder for Injection**, will remain on an allocation process. Spectrum will make reasonable attempts to fill your orders. Spectrum will be closely monitoring the distribution of FUSILEV® and **Pfizer Levoleucovorin 100 mg Powder for Injection** to help manage continued imbalances in supply.

If you have additional questions, please call 1-877-FUSILEV (1-877-387-4538). This communication and updated product information is available on the Spectrum web site at www.fusilev.com as well as on the FDA Drug Shortage web site at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

To report adverse events among patients administered **Pfizer Levoleucovorin 100 mg Powder for Injection** or **FUSILEV®**, please call 1-877-FUSILEV (1-877-387-4538). Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, or by mail using FDA Form 3500 at http://www.fda.gov/medwatch/index.html.

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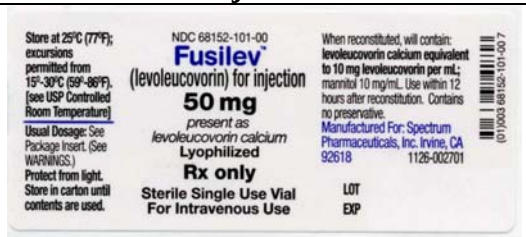
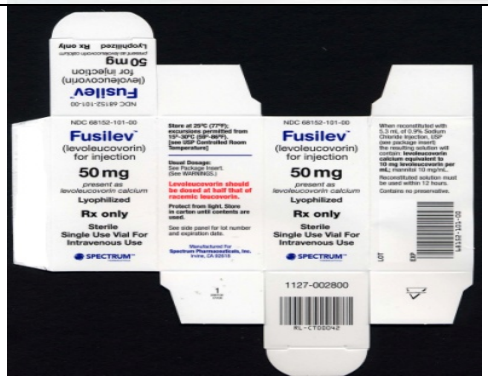
We urge you to contact our Medical Information Department at 1-877-FUSILEV (1-877-387-4538) if you have questions about the information contained in this letter or the safe and effective use of **Pfizer Levoleucovorin 100 mg Powder for Injection** or **FUSILEV®**.

Sincerely,

George Tidmarsh, MD, PhD
Senior Vice President, Chief Scientific Officer
Spectrum Pharmaceuticals, Inc.

Comparison Tables:

Labeling Component	Spectrum Labeling FUSILEV® (levoleucovorin) for Injection	Pfizer Labeling Pfizer Levoleucovorin 100 mg Powder for Injection
Vial Label		
Carton		

Spectrum FUSILEV® (levoleucovorin) for Injection	Pfizer Levoleucovorin 100 mg Powder for Injection	What does this mean to you as a Healthcare Professional?
Contains 50 mg levoleucovorin and 50 mg mannitol; sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment.	Contains 100 mg levoleucovorin and 100 mg mannitol; sodium hydroxide and/or hydrochloric acid may have been added for pH adjustment.	**Pfizer Levoleucovorin 100 mg Powder for Injection** contains two times the amount of product as FUSILEV® (levoleucovorin) for Injection. **Care must be taken to ensure that Levoleucovorin for Injection is reconstituted with the appropriate amount of solution prior to intravenous infusion to yield a levoleucovorin concentration of 10 mg/mL.**
Reconstituted with 5.3 mL of 0.9% Sodium Chloride Injection	Diluted with 10 mL of water for injectable preparations	**Care must be taken to ensure that Levoleucovorin for Injection is reconstituted with the appropriate amount of solution prior to intravenous infusion to yield a levoleucovorin concentration of 10 mg/mL.**
Is indicated for methotrexate rescue and inadvertent overdosage of folic acid antagonists. For additional information, please see the package insert.	Is indicated for methotrexate rescue and colorectal cancer. For additional information, please see the information leaflet.	In the United States, Levoleucovorin for Injection is approved only for the indications specified in the FUSILEV® package insert. The colorectal cancer indication in the United States currently is under review by the FDA.

Spectrum FUSILEV® (levoleucovorin) for Injection	Pfizer Levoleucovorin 100 mg Powder for Injection	What does this mean to you as a Healthcare Professional?
Unit of use barcode on individual vials	Original barcode omitted	The original barcode used on **Pfizer Levoleucovorin 100 mg Powder for Injection** may not register accurately on US scanning systems. Other means of confirming the correct drug is being prepared and administered to the correct patient should be utilized.
Is stored at 25°C (77°F); excursions are permitted from 15-30°C (59-86°F)	Is stored at a temperature not greater than 25°C	No impact to Healthcare Professionals – Both products can be stored at a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C.
Only available in 10 mL Type I glass vials	Only available in 20.4 mL Type I glass vials	No impact to Healthcare Professionals – Both products are available in glass vials and must be reconstituted prior to intravenous infusion.
Manufactured by Cangene bioPharma, Inc. in Baltimore, MD, USA	Manufactured by Pfizer in Catania, Italy (Establishment ID No. 3002806766)	No impact to Healthcare Professionals – Both facilities have been inspected by the FDA and are in compliance with FDA manufacturing standards.